Docket No.: HO-P02149US0
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Martin Stjernstrom

Application No.: 09/830,795 | Confirmation No.: 3545

Filed: October 29, 1999 | Art Unit: 1743

For: LIQUID MICROVOLUME HANDLING SYSTEM | Examiner: D. K. Handy

# APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within three months of the Notice of Appeal filed in this case on October 27, 2006, and is in furtherance of said Notice of Appeal.

The fees required under § 41.20(b)(2) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

## I. REAL PARTY IN INTEREST

The real party in interest for this appeal is Gyros Patent AB.

## II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

## III. STATUS OF CLAIMS

The original International application contained claims 1-9. A preliminary amendment filed with the national stage documents amended these claims and added new claims 10-13. Claims 1-13 were rejected in an office action dated October 27, 2003. In a response dated January 26, 2004, Applicant canceled claims 1-5 and 13 and amended claims 6, 8 and 12. Claims 6-12 were rejected in a final office action dated April 21, 2004. Applicant filed a request for continued examination and response on July 16, 2004 wherein claims 6-8 and 10 were amended and new claim 14 added. Claims 6-12 and 14 were rejected in an office action dated September 29, 2004. Claim 8 was then amended in a response dated January 28, 2005. Claims 6-12 and 14 were rejected in office actions dated May 3, 2005; February 8, 2006 and July 27, 2006 with no further claim amendments. An amendment after final has not been filed.

### A. Current Status of Claims

**1. Claims canceled: 1-5 and 13**

**2. Claims withdrawn from consideration but not canceled: 0**

**3. Claims pending: 6-12 and 14**

**4. Claims allowed: 0**

**5. Claims rejected: 6-12 and 14**

### B. Claims On Appeal

The claims on appeal are reproduced in Appendix A. All claims stand or fall together in this Appeal.

## IV. STATUS OF AMENDMENTS

Applicant did not file an Amendment After Final Rejection.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter relates to a method for replacing solvents for preventing samples from becoming desiccated comprising the following steps: providing a microfludic device having an open microarea for carrying a sample connected to a solvent reservoir by a microchannel; providing the sample to the microarea which sample contains one or more reactants and a solvent that is miscible with the sample; allowing the solvent to evaporate from said microarea; and continuously replacing said evaporated solvent with solvent from said reservoir. Page 6, line 28 – page 7, line 2 (Page and line numbers refer to the original Specification as filed.).

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

**A. Whether Claims 6-8, 10, 12 and 14 were properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Litborn (WO9833052) in view of Hawkins et al. (US Pat No. 5,198,353).**

**B. Whether Claims 9 and 11 were properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Litborn (WO9833052) in view of Hawkins et al. (US Pat No. 5,198,353) further in view of Mian (US Pat No. 6,319,469).**

## VII. ARGUMENT

### A. Rejection under 35 U.S.C. § 103(a) over Litborn (WO9833052) in view of Hawkins et al. (US Pat No. 5,198,353)

#### 1. Claim 6-8, 10, 12 and 14

The Patent office has improperly rejected the pending claims over a hindsight reconstruction of an embodiment of the claimed subject matter. Consequently, the Patent Office's post hoc reconstruction arguments are illogical and internally inconsistent in their attempt to rationalize using the miscible acetone from Hawkins in lieu of the immiscible cover solvent taught by Litborn.

Further, the Patent Office's combination/modification would require dramatic and nonsensical alteration to the operation of the Litborn method from an immiscible cover solvent which "locks in" the sample volume to a miscible solvent which would simultaneously dilute out a sample and quench any ongoing biochemical reactions.

The Patent Office should be reversed.

##### a. *Graham* Factors: Scope and Contents of the Prior Art

*Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), controls the consideration and determination of obviousness under 35 U.S.C. 103(a). The four factual inquires enunciated therein as a background for determining obviousness are as follows:

- Determining the scope and contents of the prior art;
- Ascertaining the differences between the prior art and the claims in issue;
- Resolving the level of ordinary skill in the pertinent art; and
- Evaluating evidence of secondary considerations.

### i. Litborn (WO9833052)

Litborn discloses a methodology for maintaining the volume of very small liquid samples:

> The basic principle is that during or in connection with the operation referred to the liquid sample is covered with a volatile liquid which is immiscible with the sample liquid.
>
> In this context "covered with" means that said volatile liquid (covering liquid) is of such a density relative to the liquid sample that it floats on top of the sample and acts as a liquid lock, or if a reversed geometry is used, the liquid sample floats on top of the cover liquid.
>
> As to the term "volatileliquid" this means that it evaporates or can be evaporated from the liquid sample without interfering or interacting with or decomposing any of the components thereof, i.e. neither the ingredients of the sample nor the solvent used.

WO9833052, pg. 5, lines 7-21. Consistent with the basic principle of operation for the Litborn disclosure, Litborn does not teach the use of a cover liquid that is miscible with the sample liquid. Office Action 08 February 2006, pg. 3 (partially bolded text).

> To compensate for the cover liquid which is evaporated during the operation in such a case supplementary or additional cover liquid is added during the operation.
>
> Said addition can be performed intermittently or continuously, continuous addition or feed being preferred.

WO9833052, pg. 8, lines 7-11.

> Generally the covering liquid is chosen so as to be substantially inert relative to the sample and also preferably relative to the reaction products from the sample.
>
> In some cases it can, however, be interesting to use a cover liquid which interacts with reaction products, e.g. waste products (gases, etc.), from the sample.
>
> In other cases it can also be of value to include one or more of the reactants to be used in the operation in said covering liquid to feed the same, even sequentially, to the reaction.
>
> Still another embodiment of the invention is represented by the case where the covering liquid is chosen so as to have the ability of extracting one or more components from the sample.

WO9833052, pg. 9, lines 23-34.

#### ii. Hawkins et al. (US Pat No. 5,198,353)

Hawkins discloses a methodology for preparing a stabilized enzyme dispersion. Some embodiments of the disclosed methods involve acetone precipitation of enzymes from solution. Office Action 08 February 2006, pg. 3. The specific working example cited by the Patent Office discloses co-precipitation of polyvinyl pyrrolidone with a protease to derive a stabilized enzyme-polymer complex in suspension. *Id.*; Column 11, lines 33-46.

### b. *Graham* Factors: Ascertaining the differences between the prior art and the claims in issue

#### i. Litborn (WO9833052)

Litborn is a distinct and unrelated method of addressing sample volume loss. Litborn discloses two immiscible liquid phases, one having a sample and one cover layer liquid which prevents sample evaporation. *E.g.* Fig. 3b. Because this cover layer liquid is selected

to evaporate quickly at or near the temperature of the sample, the cover liquid must be replaced to maintain coverage of the sample phase to prevent sample volume loss. *E.g.* Fig. 3b. In contrast, the pending claims involve maintaining a sample volume by adding miscible replacement solvent to counter ongoing sample liquid evaporation.

Litborn further discloses the possibility of using the cover layer liquid to extract, supply sample components, or "interact with".reaction products. Pg. 9, lines 23-34. The Patent Office relies upon this teaching as a suggestion consistent with using miscible acetone in place of the immiscible cover solvents clearly taught by Litborn. Office Action 08 February 2006, pg. 3; Office Action 27 July 2006, pg. 4. In the case of a cover liquid capable of extracting components of a reaction, this necessarily involves the use of a non-miscible cover fluid. The extraction process removes compounds from one phase of liquid to a second phase and occurs as reagents diffuse across a phase interface, in this case between the cover fluid and the sample solvent. The cover fluid and the sample solvent do not mix. A non-miscible cover fluid could supply reagents soluble in both phases by means of the principle of diffusion across the phase interface. Finally, the Litborn specification is not particularly informative as to what is meant by a cover solvent that "interacts with reaction products." The only example provided is a gaseous byproduct which presumably might interact with the cover fluid as it bubbles out of the sample solvent. Based on the other examples, one would infer that Litborn is referring to the possibility of reaction products soluble in both sample and cover solutions such that, as it is produced, the reaction product diffuses across the phase interface into the immiscible cover fluid. Each of these situations involves immiscible fluids and diffusion across a phase inteface. This is a completely distinct from the situation where two miscible fluids are combined in a single phase system. Applicant asserts that these cited passages in Litborn do not suggest deviating from the "basic principle" of using an immiscible cover layer fluid by substituting a miscible solvent.

### ii. Hawkins et al. (US Pat No. 5,198,353)

Hawkins is not analogous art for the field of fluid sample volume stability or microfluidic devices. MPEP § 2141.01(a). Further, when considering the problem of fluid sample volume stability, there is nothing in Hawkins disclosure of protein precipitation procedures that would "commend itself" to someone trying to solve the problem of fluid,

sample volume stability addressed by the pending application. *Id.* The Patent Office does not contest this point. Office Action 27 July 2006, pg. 3. Rather, the Patent Office claims to rely on Hawkins only "for a teaching of a solvent that is miscible with an aqueous solution." *Id.* pg 4. However, the Patent Office had previously stated its position to be:

> **One would use acetone as the covering liquid in order to precipitate out and collect (or analyze) the protein compounds without having to evaporate the sample or covering liquid. This would save processing time.**

Office Action 08 February 2006, pg. 4.

The Patent Office does not provide a cogent explanation for its modification of Litborn from the "basic principle" of an immiscible cover layer liquid to a miscible acetone "covering liquid." That there exists "a solvent that is miscible with an aqueous solution" is not a rational basis for substituting that miscible solvent for the immiscible cover liquid in Litborn. Applicant asserts that the rejection is a transparent and blatant example of impermissible hindsight reconstruction.

This retrospectively manufactured embodiment does not even make sense. In using acetone miscible with an aqueous sample liquid, there would be no "covering layer" as defined by Litborn. The purpose of the covering layer is to prevent sample volume loss due to evaporation. This allows chemical or biochemical reactions and assays to take place on a very small scale. WO9833052, pg. 6, line 29- pg. 7, line 11. Using an acetone "cover layer" to precipitate out proteins (*e.g.* DNA polymerase in a PCR reaction) from a sample for "saved processing time" would be at the cost of quenching the reaction. Thus, one of skill in the art would readily see that Litborn conceptually and expressly teaches away from the Patent Office's proposed modification. *E.g.* WO9833052, pg. 12, lines 1-3 ("Full freedom is maintained to choose the properties of the cover liquid, as long as this liquid is not miscible with the sample liquid."). The Patent Office should be reversed.

### c. Teaching, Suggestion, or Motivation to Combine or Modify the Art

To establish *prima facie* obviousness the Patent Office must identify and explain the reasons why one of ordinary skill in the art would derive the claimed subject matter. *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 2006 U.S. App. LEXIS 24642 at *10, *28-*31 (Fed. Cir. Oct. 3, 2006). *In re Lee*, 277 F.3d 1338, 1341, 1344-45 (Fed. Cir. 2002).

#### i. Modifying i. Litborn (WO9833052)by Reference to Hawkins et al. (US Pat No. 5,198,353)

##### (1) Motivation to Combine

Applicant has previously discussed how Litborn teaches away from this proposed combination. MPEP § 2141.02 (VI.) The advanced rejection is untenable for a variety of other reasons.

First, the proffered motivation is an unacceptable conclusory statement rather than the detailed explanation required by law. MPEP § 2143.01 (I.); *In re Lee*, 277 F.3d 1338, 1344-45 (Fed. Cir. 2002).

Modifying Litborn by substituting the acetone of Hawkins for the immiscible cover layer in Litborn would alter the "basic principle" of operation for the Litborn reference. Such a modification cannot support an obviousness rejection. MPEP § 2143.01 (VI.).

By adding acetone as the "covering layer" and thereby quenching any reaction through protein precipitation, etc., the modification would be incompatible with the purpose of Litborn to preserve sample volume for micro or nano liter scale chemical/biochemical reactions or assays. MPEP § 2143.01 (V.).

The Patent Office contests this last argument. Office Action 08 February 2006, pg. 4. The Patent Office reiterates the argument that use of acetone as a "cover layer" would make Litborn more efficient by eliminating the evaporation steps in Fig. 4. *Id.* Applicant does not comprehend the Patent Office's position. Litborn Fig. 4, step 2, discloses one or more evaporative concentration steps to accumulate sample constituents in a microwell. There is

obviously no counter measure for evaporative loss of sample fluid at this step. Steps 4 and 5 show addition of the immiscible sample solvent and the subsequent chemical/biochemical reaction. The main purpose of the cover liquid is to allow for a static microvolume of sample fluid for performing small scale reactions. Making the cover solvent miscible with the sample solvent in step 5 would dilute out the reaction volume and result in cross contamination of samples in multi-well devices. *E.g.* Fig. 3b. Steps 6-8 simply show that the chemical reaction products may be re-concentrated by evaporation of both solvents and the possibility of repeating the process with a new reaction solvent to perform a serial sequence of reactions. One of skill in the art assessing the Patent Office's modification with reference to Fig. 4 would readily understand the incompatibility of the proposed modification with the operation of the Litborn methods. Again, the Patent Office argument only makes sense in that it is a retrospective attempt to cobble together disparate elements to produce an embodiment falling within the pending claims.

For each of these foregoing reasons, the Patent Office should be reversed.

### B. Rejection under 35 U.S.C. § 103(a) over Litborn (WO9833052) in view of Hawkins et al. (US Pat No. 5,198,353) further in view of Mian (US Pat No. 6,319,469).

#### 1. Claim 9 and 11

The Patent Office rejections against claims 9 and 11 are founded on the rejection against claims 6-8, 10, 12 and 14 previously discussed and should be reversed on the same basis.

## VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

## IX. EVIDENCE

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the examiner is being submitted.

## X. RELATED PROCEEDINGS

No related proceedings are referenced in II. above, or copies of decisions in related proceedings are not provided, hence no Appendix is included.

## XI. CONCLUSION

Appellants have provided arguments that overcome the pending rejections. Appellants respectfully submit that the Action's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the rejection of the Action. Appellants respectfully request that the Board recommend that this application proceed to allowance.

Appellant believes no additional fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02149US0 from which the undersigned is authorized to draw.

Dated: January 29, 2007

Respectfully submitted,

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## APPENDIX A

**Claims Involved in the Appeal of Application Serial No.** 09/830,795

Claims 1-5 are canceled.

6. A method for replacing a solvent evaporating from a microvolume of sample containing solvent and reactant which are to be reacted in an open microarea of a microfluidic device comprising the step of replacing evaporated solvent continuously via a microchannel that transports solvent to the microarea from a solvent reservoir, wherein the solvent is miscible with the sample and the microvolume of solvent comprises the reactant for performing a reaction within the microvolume of solvent on the microarea.

7. The method of claim 6, wherein the microarea, microchannel and reservoir are parts of the microfluidic device.

8. A method for replacing solvents for preventing samples from becoming desiccated comprising the following steps:

providing a microfludic device having an open microarea for carrying a sample connected to a solvent reservoir by a microchannel;

providing the sample to the microarea which sample contains one or more reactants and a solvent that is miscible with the sample;

allowing the solvent to evaporate from said microarea; and

continuously replacing said evaporated solvent with solvent from said reservoir.

9. The method of claim 8 further comprising the step of anchoring the sample to the microarea.

10. The method of claim 7, wherein the reservoir is positioned so as to create an overpressure in the solvent which is in equilibrium with the interfacial pressure difference across the curved surface of the droplet or said reservoir is connected to pump means that either facilitate replacement of solvent by pumping solvent or pressurizing the reservoir.

11. The method of claim 7, wherein the microfluidic device comprises a plurality of microchannels and open chambers forming an array in the circular or rectangular format.

12. The method of claim 7, wherein one or more of the reactants are soluble in the solvent or bound to a solid support in contact with the microvolume.

13. (canceled)

14. The method of claim 8, wherein the microarea, microchannel and reservoir are parts of the microfluidic device.